REMARKS

Claims 14-23 and 26-29 are under examination. Applicants hereby amend claims 14, 19 and 26 without conceding to the Examiner's rejections and without prejudice. Support for the amendment to claims 14, 19 and 26 to include the term "human" can be found in the specification at page 1, lines 1-20, and Examples 8 and 9. Support for the term "a sole active ingredient" is found generally in the specification and especially, at page 1, lines 34-37 and at page 2, lines 6-12.

35 U.S.C. § 103

The pending claims are rejected as being obvious over Dittmar et al (U.S. 4,185,106) in view of Squiquera et al. (July 1996), Shoshan (WO 96/290455) and Thorel (FR 2,685,867). Applicants traverse this rejection.

We believe that the Examiner made an error in the Office action on page 3, second paragraph, by citing U.S.'145, as the primary reference. We assume the Examiner intended to cite U.S. '106 (hereafter Dittmar). If that is incorrect, Applicants respectfully request a telephone call to address this issue.

A rejection under 35 U.S.C. § 103 must include the teachings of all of the claimed elements, and also a teaching or suggestion to modify or combine the cited references, along with a reasonable expectation of success, to render the claimed invention obvious. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991; MPEP § 706.02(j).

The pending claims in general recite a method of treating seborrheic dermatitis in a human seborrheic dermatitis patient by administering an effective amount of a single

composition comprising a sole active component of at least one 1-hydroxy-2-pyridone and at least one surfactant.

The Examiner notes that Applicants' claims differ from Dittmar "because they are directed to a method of treating seborrheic dermatitis." Office action at 3. Applicants agree that Dittmar does not teach the treatment of seborrheic dermatitis. However, Applicants disagree that the secondary references Squiquera, Shoshan and Thorel remedy this deficiency in Dittmar's teaching.

The Examiner states that Squiquera teaches that "dandruff has been associated with a local increment in the number of pityrosporum yeasts" and that "anti-dandruff treatment can be effectively achieved with ciclopirox olamine (OCT) . . .." Office action at 3. The Examiner admits that the reference does not mention that seborrheic dermatitis has been treated with ciclopirox olamine (OCT), but alleges that it does teach that seborrheic dermatitis and dandruff are caused by Pityrosporum yeasts. *Id.* Shoshan is asserted to teach that dandruff is seborrheic dermatitis of the scalp and is associated with yeast Pityrosporum. The Examiner asserts that Thorel teaches that a combination of a 1-hydroxy-2-pyridone and undecylenic acid is effective in the treatment of dandruff or seborrheic dermatitis secondarily infected by Pityrosporum. She then states that one of skill in the art would have been motivated to combine these references to use a 1-hyroxy-2-pyridone to treat seborrheic dermatitis because its efficacy has been shown in treating "symptoms and also inhibition of [the] causative organism, Pityrosporum yeast." Office action at 4.

As noted above, the primary reference, Dittmar does not teach or disclose a method of treating seborrheic dermatitis in a human patient using a 1-hydroxy-2-pyridone. The secondary references do not remedy this deficiency.

Squiquera describes two experiments, an *in vitro* experiment which he and his colleagues performed and an *in vivo* experiment performed by Van Cutsem et al. and reported at pages 28-29 of Squiquera. Squiquera notes that *Pityrosporum ovale* (hereafter PO) has been linked to several conditions, including dandruff and seborrheic dermatitis (Squiquera at page 26) but he does not state that these conditions are caused by PO. In his *in vitro* experiment, Squiquera, tested three antifungal compounds found in shampoos marketed as active against dandruff against PO. One of these was ciclopirox olamine (OCP)[1]. Inhibition was considered positive when the halo on the agar around the PO colonies was greater then 0.3mm. Of the three compounds tested, OCP was significantly the weakest. Ketoconazole had an inhibitory effect that was 5000-fold stronger than OCP. *Id.* at 28. Thus, at page 29, paragraph 3, cited by the Examiner as support for her assertion that antidandruff treatment can be effectively achieved by OCT, the authors, in fact, note that it was ketoconazole that "produced a linear trend on a semi-logarithmic scale. This result indicates a direct relationship between the concentration of the drug (i.e., ketoconazole) and the halo of inhibition." *Id.* Squiquera teaches that in this *in vitro* test it is ketoconazole that effectively inhibits PO in a dose-dependent fashion. One of skill in the art would not read this article and take away the teaching that OCT is an effective treatment for dandruff *in vivo*, never mind for seborrheic dermatitis.

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[1] OCP and OCT appear to be used interchangeably in the Squiquera reference.

Van Cutsem, referenced by Squiquera at page 29, infected guinea pigs with PO and after 7 days the animals were said to develop severe dandruff, seborrheic dermatitis and folliculitis. Van Cutsem treated them with three agents, ketoconazole, zinc pyrithione, and selenium oxide. Again, ketoconazole was the most effective agent but this is irrelevant to the present claims which recite a method of treating human seborrheic dermatitis comprising administering a 1-hydroxy-2-pyridone. None of the compounds Van Cutsem tested was a 1-hydroxy-2-pyridone and none was tested in a human.

Moreover, the statements attributed to Van Cutsem by Squiquera do not necessarily teach that seborrheic dermatitis and dandruff are caused by Pityrosporum yeasts, as asserted by the Examiner. Van Cutsem's work was done in 1989, and although he felt it was becoming more obvious that *P. ovale* had a role in pathogenesis of certain skin conditions, he states that the exact mechanism of the pathogenic role of *P. ovale* remains to be proved.[2] Later scholarship has shown that dandruff and seborrheic dermatitis are separate conditions and that the role of PO in seborrheic dermatitis remains unclear.

As stated in the Declaration of James Leyden, M.D. (previously submitted in this application with the Request for Continued Examination filed January 5, 2006), it has been known since at least 1997 that seborrheic dermatitis is "a chronic papulosquamous dermatosis, ... and a disorder characterized by the hyperproliferation of keratinocytes in the skin. . . . It is characterized by erythema(redness of the skin)

[2] The full citation for this article can be found at footnote 12 of the Squiquera reference. This Van Cutsem article will be submitted with a Supplemental IDS soon.

scaling and yellow crusted patches. . . . Essentially, in seborrheic dermatitis, the epidermal keratinocytes multiply too quickly, causing scaling and other symptoms." Leyden at paragraphs 1 and 6.

Dandruff is a separate and distinct condition in which there is noninflammatory scaling of the scalp and the scales are thin and white or gray and different from the oily, yellowish scales of seborrheic dermatitis See paragraphs 4-6 of the Declaration of Mitchell S. Wortzman, Ph.D. (previously submitted in connection with the 09/077,194 application, to which this application claims priority, and a copy of which is attached hereto as Exhibit A).

It is unclear what causes seborrheic dermatitis. A hypothesis that "favored an etiology involving bacteria, yeasts, or both ... has remained unsupported." Dermatology in General Medicine, 5th ed., page 2 of 17 (attached as Appendix A of the Wortzman Declaration). Some in the art argue that "*P. ovale* is not the causative organism but is merely present in large numbers." *Id.* at page 3 of 17. Other possible causes of seborrehic dermatitis include drugs, neuralgic abnormalities that affect the nervous system, physical factors such as temperature and humidity and nutritional disorders. *Id.* at pages 3-4 of 17. This reference also states that "Imidazoles [e.g. ketoconazole], like other antifungal agents, have a wide spectrum of effects, including anti-inflammatory properties and inhibition of cell wall lipid synthesis. **Their efficacy is not proof of a causal relationship between *P. ovale* and seborrheic dermatitis."** *Id.* at page 10 of 17 (emphasis added). This is directly contrary to the Van Cutsem position that the effectiveness of ketoconazole is the factor that confirms his hypothesis that PO plays a causative role in dermatoses such as dandruff and seborrheic dermatitis. In view of the

uncertainty in the field about the cause, or likely causes, of seborrheic dermatitis, it cannot be said definitively that seborrheic dermatitis is caused by Pityrosporum. It is more likely, as suggested by Thorel at page 3, that pityrosporum is a secondary infection of seborrheic dermatitis. Therefore, a rejection based on the use of ciclopirox olamine *in vitro* against PO in the context of treatment of dandruff [Squiquera] is not a teaching of the effectiveness of ciclopirox olamine *in vivo* in the treatment of seborrheic dermatitis in a human.

The Examiner cites Shoshan for the teaching that "dandruff is seborrheic dermatitis of the scalp" and is associated with yeast Pityrosporum. Office action at 4. Shoshan does define dandruff as seborrheic dermatitis of the scalp once at page 1, line 7, and thereafter refers only to dandruff. However, Shoshan, which has a priority date in 1995, is mistaken to equate the two conditions. As noted in Wortzman's Declaration (Exhibit A at paragraph 4), "dandruff and seborrheic dermatitis are separate and distinct conditions", citing Appendix A (excerpts from Dermatology in General Medicine (1999)). "The rest of the scientific literature is in accord with the view that dandruff is a "noninflammatory" scaling of the scalp, while "seborrheic dermatitis is an inflammatory, erythematous, and scaling eruption that occurs in seborrheic areas." Wortzman at paragraph 5.

Therefore, references which treat dandruff do not have the required suggestion to use the teachings for seborrheic dermatitis. Further, and importantly, Shoshan teaches a composition that is a combination of at least one cytotoxic agent and at least one antifungal agent, among which can be cicloproxolamines. Shoshan, however, does not teach or suggest that cicloproxolamine, or any 1-hydroxy-2-pyridone, can be used

as the only active ingredient in the treatment of dandruff or seborrheic dermatitis. Therefore, Shoshan cannot make up for the deficiencies of Dittmar in view of Squiquera.

Thorel is cited by the Examiner as a "teach[ing of] a combination of 1-hydroxy-2-pyridone and undecylenic acid [for] the treatment of dandruff or seborrheic dermatitis secondarily infected by Pityrosporum." Thorel, however, not only requires the use of undecylenic acid with the 1-hydroxy-2-pyridone but states that "the association of the two product families . . ., involve an unpredictable synergistic effect when the resulting effects are compared to those of the components taken separately." *See* Page 3, lines 7-10. Thus, Thorel teaches away from the use of either component alone. Applicants' claims are all limited to a single active component, 1-hydroxy-2-pyridone. Therefore, Thorel also cannot cure the deficiencies of Dittmar in combination with Squiquera and Shoshan.

The Federal Circuit has clearly stated that the evidence of motivation or suggestion to combine must be "clear and particular." *In re Dembiczak*, 175 F. 3d 994, 999, 50 USPQ2d 1614,1617 (Fed. Cir. 1999). The Examiner can satisfy the burden of establishing a *prima facie* case of obviousness "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071,1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988) (emphasis added).

There is no objective teaching in the cited references to teach or suggest the use of 1-hydroxy-2-pyridone as the sole active component in the treatment of seborrheic

dermatitis in a human patient. The Examiner has acknowledged that Dittmar does not teach a method of treatment of seborrheic dermatitis. The combination of the teachings of Shoshan and Thorel with Dittmar would not lead to the claimed invention because both of the secondary references require the use of two active compounds in the treatment of the skin conditions described therein. Lastly, the objective teaching of Squiquera is that ketoconazole is effective in the treatment of dandruff in an *in vitro* assay. Moreover, Squiquera does not teach or suggest a method of treatment of seborrheic dermatitis in a human using ciclopirox. The poor showing of the effectiveness of ciclopirox in Squiquera's *in vitro* assay combined with the teachings of Thorel and Shoshan, which teach away from the use of ciclopirox as the sole active compound, would not lead one of skill in the art to try that compound alone in the treatment of seborrheic dermatitis and would not give rise to a reasonable expectation of success.

At best, and for purposes of argument only, even if one might try to treat seborrheic dermatitis using only 1-hydroxy-2-pyridone, a determination of obviousness based on what the skilled person might find obvious to try cannot be a basis of support of an obviousness rejection. *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.2d 1361, 1371, 56 USPQ2d 1065,1075 (Fed. Cir. 2000). Rather, the proper test requires determining what the prior art would have led the skilled person to do. *Id.*

Applicants respectfully request the removal of this § 103 rejection.

CONCLUSION

In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is not rendered obvious in view of the prior art references cited against

this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of pending claims 14-23 and 26-29.

Finally, should any outstanding issues remain, Applicants respectfully submit a request for a personal interview with the Examiner.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: September 7, 2006

Attachments: **Attachments** to this amendment include:

Exhibit A, Declaration of Mitchell S. Wortzman, Ph.D.